PATHOLOGY OF THE PNEUMONIA FOLLOWING INFLUENZA

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Contributions to the study of the pneumonia following influenza in the recent epidemic are still desirable because of the difference of opinion as to its nature and causes that has been evidenced by numerous published papers. All have agreed as to the uniform character of the disease influenza wherever it has appeared in its swing across the continent, but conflicting views have been presented as to its etiology and as to the relation of various bacteria discovered in the respiratory tract, especially in cases of pneumonia, to the original disease and to the pneumonia. The dispute is concerned more particularly with the part played by the *Bacillus influenzae* of Pfeiffer, which some authors have found so regularly present as to lead them to consider it the cause not only of the pneumonia but also of the original epidemic disease influenza. Indeed, it was launched by Pfeiffer as the cause of influenza. Investigators in other localities have failed to find this organism, and this has been explained by those more successful as being the result of technical incompetence.

The present study was made by a commission consisting of Major R. A. Kinsella and myself, sent by the Surgeon-General of the United States Army, first to Camp Lee in Virginia and later to Camp Dix in New Jersey. Twenty necropsies were performed at Camp Lee when the epidemic was nearing its height, and twelve at Camp Dix at a time when the influenza was practically over but many cases of pneumonia were still in the hospital. Between these visits and afterward, seventeen necropsies were performed at the Johns Hopkins Hospital on patients who died there in the early part of the epidemic of influenza.

It has been stated that the influenza bacillus may be present in the upper respiratory tract, larynx and bronchi when it is not to be obtained from the substance of the lung. On this account, cultures and smears are made from bronchial pus, from the mucosa of the trachea, larynx, etc. This precaution was not observed in the Camp Lee cases, although cultures were made from the accessory nasal sinuses whenever possible; but it was carried out at Camp Dix and later at the Johns Hopkins Hospital. It was suggested that this might account for our inability to find the influenza bacillus in all the cases at Camp Lee; but the later study of these cases has proved this to be unfounded. A combination of Goodpasture's and Weigert's stain[1] permits a very satisfactory survey of gram-negative and gram-positive bacteria in the tissues. The organisms are brilliantly stained, the gram-negative red, the gram-positive blue, black or purple, so that it is easy to recognize the presence of influenza bacilli even when a few are mixed with great numbers of gram-positive bacteria. This stain showed that influenza bacilli, when they occurred in the bronchi at all, penetrate into the smaller bronchioles and could hardly be missed in a culture taken from the lung unless the medium employed for the culture was unsuited to their growth. The morphology of the influenza bacillus when clearly seen in the tissues or in smears is very characteristic, and their discovery in this way was nearly always confirmed by reference to the records of the cultures. Indeed, the morphologic recognition of the predominant organisms in the tissues seemed surprisingly accurate when compared later with the results of the cultures.

The accompanying table gives the predominant organism in each case, as decided by consideration of smears, cultures and sections usually with the aid of mouse inoculations. The influenza bacillus is recorded in the table whenever found even in small numbers or in the trachea or nasal sinuses alone. When it was the predominant organism it is put first.

Some doubt may be admitted as to the nature of these bacilli in certain cases, and Colonel Nichols has pointed out the occurrence of members of the Fried-

1. MacCallum, W. G.: A Stain for Influenza Bacilli in Tissues, J. A. M. A. **72**: 193 (Jan. 18) 1919.

länder group. In Cases 85 and 87 it was thought that the bacilli resembled the Friedländer bacillus in culture.

From the table it is seen that at Camp Lee most of the cases showed Pneumococcus Type IV without any influenza bacilli. This conclusion is not reached from the mere failure of cultures but from the examination of smears from the lung and stained sections from lung, bronchi and trachea, often including also the larynx and nasal sinuses. No considerable number of influenza bacilli could be overlooked, and it has been observed repeatedly that they are not made to disappear by even an overwhelming growth of other bacteria. They were definitely found in three cases, and

RESULTS OF BACTERIOLOGIC EXAMINATIONS*

Camp Lee		Johns Hopkins Hospital		Camp Dix	
Case No.	Bacteria Found	Case No.	Bacteria Found	Case No.	Bacteria Found
211	St, B I	5706	S H	80	B I, St
212	Pn I	5712	Pn IV	81	B I
213	Gas bacillus	5713	Pn IV, St	82	Pn, B I
214	B I, Pn	5714	Pn IV, St	83	Pn, B I
215	Pn, B I?	5720	S H	84	Pn IV, B I
216	Pn IV, B I	5724	St, Pn	85	Pn IV, B I?
217	Pn	5725	Pn	86	B I
218	Pn IV, B I?	5726	Pn	87	Pn IV, B I?
219	S H	5728	Pn IV	88	Pn III, B I
220	Pn IV	5733	Pn, St	89	B I, S H
221	Pn IV	5736	Pn, St	90	B I, Tb, Pn
222	Pn IV			91	B I, Pn
223	Pn IV	5753	Pn		
224	Pn IV	5763	Pn IV		
225	Pn IV	5765	Pn		
226	Pn, S H, St	5766	Mixture		
227	Pn IV	5769	Pn, mixture		
228	Pn IV				
229	Pn IV				
230	Pn IV, B I?				

* St indicates staphylococcus; B I, Bacillus influenzae; Pn I, pneumococcus Type I; S H, Streptococcus hemolyticus; Tb, tubercle bacillus; Mixture, masses of bacteria of all kinds.

there were in three other cases a few gram-negative bacilli which might be thought to be influenza bacilli. At the Johns Hopkins Hospital similar methods revealed no influenza bacilli whatever. At Camp Dix, on the contrary, influenza bacilli were found in every case.

From these results it seems necessary to draw one of two conclusions: In certain regions or in certain communities the influenza bacillus may be so prevalent as a relatively harmless inhabitant of the throat that when some epidemic disease, such as influenza, lowers the resistance of many persons, it becomes the natural secondary invader capable of producing pneumonia.

This might be regarded as the endemic occurrence of a potential cause of pneumonia.

On the other hand, it has been shown that a single carrier of the hemolytic streptococcus, when introduced into a hospital ward full of patients with measles, may be the source of an epidemic of streptococcus pneumonia. It seems quite probable that secondary infection with the influenza bacillus with the production of pneumonia may in the same way have a local epidemic character.

No satisfactory evidence has been brought forward to show that the epidemic disease influenza is a bacterial infection. It is evidently a general or systemic infection not especially affecting the respiratory tract and analogous in many respects, as Bloomfield has pointed out, to the well known acute exanthematic diseases. It produces an extreme depression of the general resistance of the individual to the invasion of bacteria, as is shown in one respect by the characteristic leukopenia, which may persist in spite of the development of pneumonia. Under these circumstances, bacteria that are present in the throat or are introduced from without readily invade the tissues of the whole respiratory tract and give rise to pneumonia. Because of the lack of resistance, they multiply until they are present in such enormous numbers as are never seen under ordinary conditions. This must be regarded as a secondary infection. The secondary infection apparently determines the anatomic type of the pneumonia, but there may be other successive infections with different organisms, so that it often becomes difficult to say which is the secondary and which the tertiary or quaternary infection. It seems possible that one or more of these organisms may be present without producing any recognizable lesion, while a later invader causes pneumonia, or that when one organism has produced its characteristic pneumonia, others may grow beside it without altering the lesion. On the other hand, a final invader may completely mask the original pneumonia by producing a widespread necrosis.

The influence of the predisposing disease, influenza, is such as to permit the extremely rapid growth of the organisms and minimize the reaction of the tissues. Any attempt to recognize the nature of the infecting

organisms on the basis of our knowledge of the specific anatomic effects that they produce in ordinary times must be made with this in view.

It is perhaps questionable whether we have as yet enough carefully studied cases of pneumonia produced by unmixed infections with each of the bacteria concerned, on the basis of predisposing influenza, to allow us to decide as to the precise anatomic effect that is characteristic of each. Thus it is probably impossible to distinguish a Type I pneumococcus pneumonia from one produced by pneumococcus Type II. It is difficult to say whether *Staphylococcus aureus* produces, under these circumstances, a pneumonia that is distinct from these, although many cases have been studied and it is possible that some criterion will be found that will aid in making this distinction. Those produced by the hemolytic streptococcus are probably recognizable as such, and it appears that when alone or as the predominant organism the influenza bacillus of Pfeiffer produces an interstitial bronchopneumonia that is definitely and easily distinguished from all the others. The difficulty in making these distinctions may be due in part to the fact that mixed infections are the rule.

At the Johns Hopkins Hospital and at Camp Lee we observed patients in an early stage of the epidemic, evidently those of great susceptibility, who succumbed quickly to pneumonia. At Camp Dix the epidemic that had raged with high mortality was practically over, and deaths were occurring among those who had survived somewhat longer and were beginning to present evidences of late extensions of the secondary infection in the form of pleurisy with effusion, endocarditis, scattered infarcts, etc. It seems that the performance of a series of necropsies in one place throughout the whole course of an epidemic might result in this way in revealing all the successive stages of the disease.

TYPES OF PNEUMONIA

In persons who have just passed through an attack of influenza, the following types of pneumonia may be recognized, although it is evident that the distinctions may be rendered indefinite by simultaneous infection with other organisms: Pneumonia caused by (1) the

pneumococcus; (2) the staphylococcus; (3) the streptococcus, and (4) *B. influenzae* of Pfeiffer.

1. *Pneumococcal Pneumonia.*—When the pneumococcus occurs in pure culture, and also in those cases in which it is the predominant organism even in the presence of influenza bacilli and other organisms, a characteristic form of pneumonia is produced under the conditions of lowered resistance. In most instances there is very little fluid in the pleural cavity, and the surface, instead of being covered with a shaggy exudate of fibrin, is only slightly dulled. There are brick-red, paintlike patches here and there, and sometimes small, elevated, grayish yellow flecks which become confluent in patches. The pleura and interlobular septums and remaining framework of the lung appear to be unchanged. The bronchi are not especially conspicuous. Their walls are not thickened, and while they may sometimes contain in the later stages fibrinous molds, they are usually empty or partly filled with a thin, brownish or blood-stained, frothy fluid. Their mucosa shows no marked alteration from normal. The blood vessels are normal.

On external inspection of the lung, it is frequently possible to recognize sharply outlined consolidated lobules alternating with air-containing and atelectatic lobules. The lobular character of the consolidation is in these cases well marked, although it tends to lose its definiteness through the confluence of adjacent areas. No general statement can be made as to the location of the consolidation, but it usually affects the posterior and lower part of each lobe, and the posterior part of the lower lobe is especially frequently involved.

The cut surface of the lung shows in the more acute cases a peculiar lobular or confluent consolidation which corresponds well with what is commonly written of the stage of engorgement in the description of lobar pneumonia. Bronchioles, blood vessels and the framework of the lung are not appreciably altered. The substance of the lung is firm, elastic, and not rigid as in later stages; but it pits on pressure, exuding a great quantity of blood or brownish blood-stained fluid. The surface is smooth, moist, slightly elevated above the surrounding tissue, grayish red or brownish red, and coarsely spongy. Distinct but minute depres-

sions can be seen everywhere, filled with a translucent, gelatinous, red fluid. These are too large to be the cavities of alveoli, and are separated by what appear to be thick walls of homogeneous tissue. They are in fact the widened ductuli alveolares filled with fluid and separated by areas of alveoli filled with a somewhat firmer exudate. No visible or palpable plugs of exudate project from any part of the surface, and there is nothing of the roughness that this produces in later stages. Nevertheless, the consolidated tissue is easily distinguished from that surrounding it, because it has lost the satiny texture of the normal lung, which may be pulled this way and that, like silk gauze. In the area of pneumonia, despite its smoothness and moist, rather translucent surface, the distended form of the meshes is maintained.

Microscopically these areas show an extraordinary dilatation of the ductuli alveolares, which are filled with clear fluid containing only a few leukocytes and a delicate coagulum. They are lined with a curious hyaline substance which begins in a layer overlying the cylindric epithelium in the terminal part of the bronchiole and often runs over the orifices of the atriums or enters them and extends toward the air sacs. It does not give the reactions of fibrin. The alveoli contain an exudate of fluid with a few leukocytes and mononuclear cells, often overshadowed by great numbers of well preserved red corpuscles. These cells are held together by the most delicate, filmy network of fibrin. Great numbers of pneumococci are scattered throughout the exudate. The alveolar walls maintain their normal appearance.

Later stages in the pneumonia show within these areas patches of rough, gray, consolidated tissue, from which definite plugs of exudate project. Every transitional stage may be found, up to the most advanced lobar consolidation, with dense gray hepatization.

2. *Staphylococcal Pneumonia.*—We encountered no cases in which the staphylococcus was present alone and, indeed, none in which it occurred in very great numbers. No definite statement may be ventured as yet, therefore, regarding the type of pneumonia produced. In one case in which the staphylococcus appeared to be the predominant organism, the lesion

was indistinguishable from that just described for the pneumococcus.

3. *Streptococcal Pneumonia.*—When *Streptococcus hemolyticus* occurs alone in these cases, as in Cases 219 and 5720, the lesion produced is practically identical with that described as "lobular pneumonia" in certain cases of the previous epidemic. There is not necessarily extensive pleural effusion, but the pleura may contain a small amount of blood-stained fluid. The interlobular septums are edematous, and the bronchial walls are slightly thickened. The area of consolidation is indefinitely outlined, and in places it is deep red or almost black, evidently as the result of laking of blood.

Microscopically the bronchi and alveoli are packed with leukocytes, blood and fibrin, and loaded with tangled masses of streptococci. Much of the blood is laked and appears in the form of shadows. Much of it, again, is coalescent into a beaded network of pink-staining, hyaline material. The capillaries in the alveolar walls are plugged in many places with hyaline fibrinous thrombi, and a similar hyaline material is found in the walls of the larger blood vessels. The bronchial walls are infiltrated with leukocytes, and the epithelium is lifted up or destroyed. Whole areas of the lung, although retaining their form, are entirely necrotic, the alveolar cavities being packed with almost solid masses of streptococci. Lymphatics are everywhere distended with exudate containing enormous numbers of streptococci. In none of these cases was there enough resistance to give time for the development of an interstitial bronchopneumonia.

4. *Pneumonia Produced by Bacillus Influenzae of Pfeiffer.*—In two cases at Camp Dix the influenza bacillus was present in pure culture, and in others it was the predominant organism. Tissues from another case in which the influenza bacillus occurred alone were sent me from Camp Jackson. It is easy to recognize the type of pneumonia produced by this organism, since it is fundamentally different from the others.

There is no abundant pleural exudate, although the pleural surface may be covered with fibrin or with old adhesions. The bronchi exude a thick, yellow pus, and the bronchial glands are moderately enlarged.

On section, the lung is found to be in large part air-containing, but it is studded throughout with palpable shotlike nodules or with somewhat larger patches of firm consistency. The cut surface of these nodules is smooth, and they are grayish yellow. They are seen to be peribronchial, so that when they stand alone the center is occupied by the lumen of a bronchiole. The remaining lung substance is air-containing or indurated and grayish.

Microscopically it is found that the brŏnchi are filled with an exudate of leukocytes, among which numerous influenza bacilli are lying, sometimes in clumps and scattered freely, but most often enclosed in phagocytic cells. The wall of the bronchus is greatly thickened by infiltration of mononuclear cells with a few leukocytes, and by the new formation of connective tissue cells. The alveolar walls for a considerable distance about this are similarly thickened, infiltrated and indurated. The alveoli contain an exudate which is usually rich in leukocytes, but which is often predominantly composed of desquamated epithelial cells and dense fibrin. In this exudate it is rarely possible to find influenza bacilli. Organization is advancing rapidly, and in many instances it has completely replaced the fibrinous exudate with fibrous tissue over which epithelial cells have grown.

The lymphatic channels in the bronchial walls and the widened interlobular septums are inconspicuous, and none are found distended with exudate. There is no intense infection of the pleura or great outpouring of exudate. These two facts, together with the relatively inconspicuous part played by the polymorphonuclear leukocytes in the alveolar exudate, and in the exudate infiltrating the walls of the bronchi and alveoli, are all that distinguish this pulmonary change from the interstitial bronchopneumonia caused by the hemolytic streptococcus, as described in previous papers. The sharp contrast between this form and those produced by the pneumococcus and streptococcus is very evident.

In describing the forms of pneumonia caused by the hemolytic streptococcus, it was shown that interstitial bronchopneumonia was produced when the organisms encountered a high resistance, through which the tissues succeeded in barricading themselves

against invasion and repressing the multiplication of the bacteria, but that with a lapse in the powers of resistance there might be produced in the same case areas of lobular pneumonia in which an exudate of leukocytes filled the alveoli. In this exudate the streptococci multiplied with great rapidity.

In the case of the influenza bacillus an exactly analogous condition exists. There are cases in which an interstitial bronchopneumonia has developed, with restriction of the bacilli to the bronchial exudate, but in which later, probably with lowering of resistance, other lesions presenting the character of lobular pneumonia have arisen in which the more distant alveoli are packed with leukocytes with abundant influenza bacilli.

In the doubt that for a time assailed me as to whether the interstitial form of bronchopneumonia seen in Texas might after all be due to the influenza bacillus rather than to the predominant streptococcus, I have been much reassured by this finding. Although influenza bacilli were found as accompanying organisms in a few of those cases, there were many in which the typical lesions were produced by the streptococci alone. But now that it appears that streptococci and influenza bacilli may in precisely similar ways be governed, as regards the character of the lesions they produce, by the resistance opposed to them, it seems unnecessary to ascribe one type of lesion to the streptococcus and another to the influenza bacillus.

Various complications that occurred in these cases of pneumonia will be discussed in detail in another paper. They include such things as hyaline degeneration of the rectus abdominis muscles, ulcerative laryngitis and tracheitis, and generalized emphysema.

CONCLUSIONS

1. The epidemic disease influenza resembles in many respects measles and other acute exanthematic diseases. Nothing is definitely known as to its causative agent.

2. It produces great lowering of resistance to bacterial invasion and is therefore often followed by pneumonia caused by the different types of pneumo-

coccus, *Staphylococcus aureus, Streptococcus hemolyticus* or the influenza bacillus of Pfeiffer.

3. In some regions the influenza bacillus is a particularly common secondary invader. In other regions it is insignificant, its place being taken by one of the pneumococci. This may depend on an endemic or epidemic distribution of these organisms as inhabitants of the nasopharynx.

4. The form of pneumonia produced after influenza is greatly modified by the lowering of resistance, which allows huge numbers of bacteria to grow. Nevertheless the types caused by the pneumococcus, streptococcus, and influenza bacillus are to be sharply distinguished. Probably the type caused by the staphylococcus will be shown to have distinctive peculiarities when adequate material has been studied.

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